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Feasibility and safety of a 12-week INR follow-up protocol over 2 years in an anticoagulation clinic: a single-arm prospective cohort study

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Abstract

The 2012 American College of Chest Physicians' guidelines recommended a 12-week INR follow-up interval may be appropriate for patients on stable warfarin doses. Limited evidence supports this recommendation. A single-arm, prospective cohort study over 24 months was completed in a Veterans Affairs anticoagulation clinic to determine the long-term feasibility and safety of implementing an extended INR follow-up interval in Veterans on stable doses of warfarin. Participants were required to have a stable warfarin dose for 6 months prior to enrollment. A prespecified protocol was used to titrate, extend, and manage the INR interval up to 12 weeks. Scheduling of extended INR intervals was a primary outcome. Safety outcomes included major and serious bleeding and thromboembolic events. A post-hoc comparison of baseline characteristics between individuals who were scheduled for at least 4 consecutive 12-week INR follow-up intervals and those who were not was completed. Of the 50 participants, 36 (72%) were scheduled for at least one 12-week interval and 15 (30%) were scheduled for 4 consecutive intervals. There were 2 thromboembolic events that occurred in 1 participant. There were 28 major and serious bleeding events in 19 participants; 8 occurred while on the extended INR interval. In the post-hoc analysis, no participants scheduled for 4 consecutive 12-week intervals had heart failure. Based on 2 years of monitoring, a 12-week INR follow-up interval using a detailed protocol with titration of INR interval extension appears feasible for a subset of patients. Patients with heart failure may not be suitable for this intervention.

Keywords Anticoagulation · Drug monitoring · International normalized ratio · Time factors · Warfarin

Highlights

- 72% of participants were scheduled for at least one 12-week interval and 30% were scheduled for 4 consecutive intervals
- A 12-week INR follow-up interval using a detailed protocol with titration of INR interval extension appears feasible for a subset of patients. However, risk versus benefit should be assessed with an understanding that warfarin dose and INR stability may not be maintained
- Patients with heart failure may not be suitable for a 12-week INR follow-up interval
- This study can be used to power a future randomized controlled trial to validate the safety and effectiveness of an extended INR interval

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Introduction

Despite warfarin's use since the 1950s, it still requires frequent lab monitoring to ensure a balance between bleeding and thromboembolic risk [1]. Direct oral anticoagulants (DOACs) are often preferred over warfarin and are being used more frequently in clinical practice due to their predictable response, lack of monitoring required, and fewer food and drug interactions [2–4]. However, some patients are unable to use DOACs due to their indication for anticoagulation while some patients prefer warfarin due to the regular contact with health care providers and frequent monitoring [3, 5–7]. There is limited evidence available to guide clinicians on an ideal INR follow-up interval for patients with stable warfarin doses. Many clinicians in the United States use 4–6 week INR follow-up intervals for these patients [8–10]; however, the 2012 American College of Chest Physicians' guidelines suggested a 12-week INR follow-up interval may be appropriate [11]. An extended INR follow-up interval has the potential to decrease cost and workload for both the healthcare system and patients [12].

There are two clinical studies evaluating a 12-week INR interval. Schulman et al. conducted a randomized controlled trial on INR duration and found 12-week follow-up to be non-inferior to 4-week follow-up [13]. However, all patients were contacted by their warfarin provider every 4 weeks regardless of their randomization status. Carris et al. implemented a 12-week INR follow-up interval for a maximum of 68 weeks and found that few patients were able to maintain a 12-week interval [12]. Patients with nontherapeutic INRs, considered to be >0.3 away from goal, warfarin dose changes, and shorter follow-up intervals required were removed from further observation in the study after the initial visits.

Compared to previous studies, this study included a patient population with longer baseline warfarin stability, detailed inclusion and exclusion criteria, and a longer duration for all patients. This study reflects an ideal but pragmatic approach for extending an INR follow-up interval to 12 weeks in an anticoagulation clinic while allowing participants to remain in the study and requalify for an extended follow-up interval despite situations occurring such as nontherapeutic INRs, procedures, and drug interactions. The objective of this study was to determine the feasibility and safety of implementing an extended INR follow-up interval for a 2-year period in Veterans on a stable dose of warfarin. It was hypothesized that this intervention could be implemented and patients could be maintained on an extended INR follow-up interval.

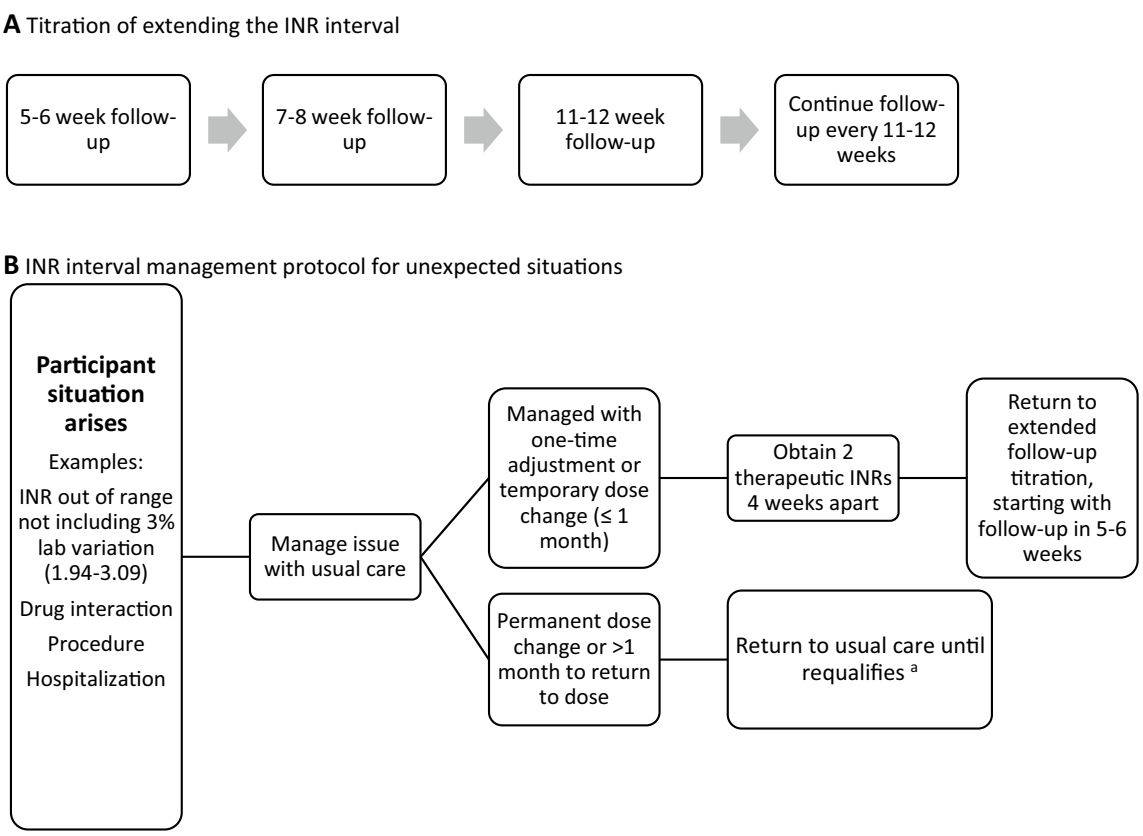
Methods

This single-arm, prospective cohort study evaluated the feasibility and safety of a protocol to extend the INR interval up to 12 weeks over 2 years. A detailed explanation of the study methods is described in Porter et al. [14]. The study took place in a pharmacist-managed anticoagulation clinic under the guidance of a hematologist medical director. In this clinic, pharmacists have prescriptive authority under a scope of practice where they assess patients independently and manage anticoagulant therapy. This study was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board (IRB) and the William S. Middleton Memorial Veterans Hospital Research and Development Committee. An independent Data Monitoring Committee (DMC) monitored the safety of the study.

The following inclusion criteria was used: 18 years of age or older, on indefinite warfarin therapy, a target INR goal of 2.0–3.0, a patient of the anticoagulation clinic for the previous 12 months, and a stable weekly warfarin dose for the prior 6 months, with no more than a single, one-time adjustment [14]. A planned interruption for a procedure or surgery with INRs out-of-range during that time would not exclude a patient from the study. Patients were excluded if they had: at least one episode of consumption of 4 or more alcoholic beverages in 24 h in the previous 6 months, diagnosis of cancer and on active chemotherapy or radiotherapy in the previous 3 months, life expectancy of less than 1 year, enrolled in other investigational drug protocols, only received care in the Anticoagulation Clinic for part of the year (i.e. patients who are managed by another clinic for the winter), received visiting nurse services for INR monitoring, thrombocytopenia with platelet count of less than 100 K/μL in the previous 12 months, history of bleeding or thromboembolism requiring medical intervention within the previous 6 months, treatment for active liver disease, diagnosis or documentation in the electronic health record suggesting cognitive impairment, activated power of attorney, inability to provide informed consent, non-English speaking, an unstable mental health disorder that impairs judgment which had specific criteria and was flagged in the electronic medical record, or a history of nonadherence to anticoagulation clinic policies and procedures, such as missed appointments, self-adjustment of warfarin dose, or noncompliance. Eligible patients were invited by a pharmacist staff member and interested patients underwent informed consent.

Intervention

Once patients were enrolled in the study, their INR interval was adjusted per the protocol as described in Fig. 1a.



[a] A participant requalified for an extended interval when they were on the same warfarin dose for at least 6 months, except for a single, one-time dose adjustment and did not meet any exclusion criteria.

Adopted with permission from Porter AL, Margolis AR, Schoen RR, Staresinic CE, Ray CA, Fletcher CD. Use of an extended INR follow-up interval for Veteran patients in an anticoagulation clinic. *J Thromb Thrombolysis*. 2017;43(3):318-325.

Fig. 1 Extended INR interval protocol

For a detailed explanation of how patients were titrated to 12 weeks, please see Porter et al. [14]. The only difference between usual care provided by the anticoagulation clinic and the study intervention was the extended duration of the INR interval.

If certain situations arose where an extended INR interval was no longer appropriate, participants returned to usual care (Fig. 1b). If there was a permanent weekly warfarin dose adjustment or if the temporary dose change was more than 1 month, the participant would continue with usual care management. However, participants could requalify for an extended interval if they were on a consistent weekly warfarin dose again for at least 6 months, except for a single, one-time adjustment. Planned procedures with INR(s) out of range would not exclude a patient from requalifying. In situations where there was not a permanent weekly dose adjustment or if the temporary dose change was less than or equal to 1 month, the patient returned to an extended INR interval after obtaining two therapeutic INRs 4 weeks apart (Fig. 1b). A 24-month study monitoring period allowed sufficient time for a participant to requalify for an extended INR follow-up interval after management of a situation requiring return to usual care (Fig. 1b).

Participants also returned to usual care if they met any exclusion criteria throughout the study with several exceptions. If the exclusion criteria had a time frame associated with it (e.g. major bleeding or binge drinking in previous 6 months) and that issue was resolved for the prespecified time frame, then the participant was eligible to resume extended INR intervals. A participant was also no longer eligible for the protocol if his or her INR goal changed from the study's required goal of 2.0–3.0. If a situation arose where it was no longer appropriate to extend a follow-up interval, the protocol for unexpected situations (Fig. 1b) was followed. However, of the 634 participant visits eligible for extended intervals, 94.3% were scheduled for the correct INR interval per quality assurance review. Of the protocol deviations, 3.0% of the deviations were too short and 2.7% were too long of an interval between visits. Adherence rate to the protocol was consistent throughout the study duration.

Variables

The purpose of this study was to determine the potential implementation barriers of an extended INR interval protocol, and the primary outcome measured the feasibility of designing a larger study. The number of participants who were scheduled for a 12-week interval of follow-up was determined along with the duration that interval could be maintained. Secondary feasibility outcomes included permanent warfarin dose changes and participant change in eligibility status (i.e. no longer on warfarin through the anticoagulation clinic, INR goal changed, met an exclusion criteria). Change in time-in-therapeutic range (TTR) was calculated with the Rosendaal method [15].

Protocol safety was a secondary outcome of the study. The primary safety outcome was bleeding and thromboembolic events. Major bleeding was defined as a fatal or symptomatic bleed into a critical area or organ, bleeding leading to hospitalization, or transfusion of two units or more of packed red blood cells [14]. This measure is the standard definition used by the anticoagulation clinic for event reporting. Attribution of safety events was determined by considering if the patient was on an extended interval, their INR value, and the relationship to hemostasis at the time of the event (see Table 1 for levels of attribution definitions). Safety was also measured through the frequency of critically low (<1.5) or high (≥ 4.5) INRs while the patient was on an extended interval.

Data collection

Study outcomes were collected at baseline and at 6, 12, and 24 months. Information was extracted from the electronic health record retrospectively in duplicate by two independent investigators. In the case of discrepancies between the duplicate extractions, a third investigator adjudicated if needed. Study staff used a note template when interacting with participants to facilitate data collection. Participant data collection was stopped earlier than 24 months for participants who met an exclusion criterion without a time frame associated with it (i.e. no longer on warfarin through the anticoagulation clinic, INR goal changed). Reportable events, including serious adverse events, were reported to the IRB and DMC when they occurred.

Data analysis

As this was a feasibility study to potentially inform a future randomized controlled trial, the target sample size was a minimum of 50 patients and a maximum of 75. The sample size was determined based on projected clinic resources. The paired Wilcoxon Signed Rank Test was used to compare continuous and ordinal variables from baseline to 6, 12, and 24 months post-enrollment. All comparisons were made using the same time duration (i.e. 6 months pre-intervention versus 6 months post-intervention). To be included in the modified intention-to-treat analysis, participants needed to have an INR drawn at some time during the time period (INR monitoring may not have occurred during the entire time period). A per-protocol sensitivity analysis was also conducted including participants whose INR was monitored through the full duration of the assessment period.

A post-hoc analysis was conducted assessing those who achieved four consecutive 12-week intervals. An assessment of their changes in TTR was completed using the Wilcoxon Signed Rank Test and a comparison of baseline characteristics to those who did not have four consecutive 12-week intervals was completed using the Mann–Whitney *U* Test and the Fischer's Exact Test. There was no adjustment for repeated tests and all analysis used an alpha level of 0.05 for consideration of statistical significance. Stata version 14.2 was used for the statistical analysis.

Results

Of the 257 eligible patients, 107 were invited to participate and 51 enrolled in the study during the intensive 3-month enrollment period [14]. Patient enrollment was from March to June 2015 across six anticoagulation clinics within a health system.

Of the 51 participants who enrolled, one participant withdrew from the study prior to receiving an extended INR follow-up interval and was not included in the data analysis (Fig. 2). Overall, 39 participants completed the 24-month study duration. Reasons participants were withdrawn from the study included discontinuation of warfarin (four participants), transfer of care out of the health system (six participants), and change in INR goal (one participant).

The 50 participants who initiated the study protocol were primarily white, non-Hispanic males (98%, 98% respectively). Table 1 describes baseline demographic information. There was a low incidence of bleeding at baseline (12 months prior to enrollment), as there were only four serious bleeding events across two participants. There were no major bleeding or thromboembolic events. No enrolled participants had GFR <30 mL/min/1.73 m^2, with 22% having a GFR of 30–59 mL/min/1.73 m^2 and 78% with a GFR >60 mL/min/1.73 m^2. The proportion of patients taking at least one antiplatelet was 54%, with 46% taking aspirin, 4% taking clopidogrel, and 4% taking both aspirin and clopidogrel.

Of the 50 participants, 36 (72%) were scheduled for at least one 12-week interval, 27 (54%) were scheduled for 2 consecutive intervals, and 15 (30%) were scheduled for 4 consecutive intervals (Table 2). There were 24 (48%)

Table 1 Feasibility and safety outcomes (n = 50)

Feasibility	n (%)
Participant scheduled for at least one 12-week interval	36 (72)
Participant scheduled for at least 2 consecutive 12-week intervals	27 (54)
Participant scheduled for at least 4 consecutive 12-week intervals	15 (30)
Participant scheduled for 9 consecutive 12-week intervals	3 (6)
Participant experienced a warfarin dose change	24 (48)
Required 6 or 12 months of usual care due to meeting an exclusion criteria with a time requirement	9 (18)
Participant removed from the study (due to exclusion criteria or withdrew)	11 (22)
Participant met any exclusion criteria during study	17 (34)
Safety	
INR ≥ 4.5 while on an extended interval[a]	1 (2)
INR < 1.5 while on an extended interval[a]	3 (6)
TE events (# events)	2
# of participants with TE	1 (2)
# of events with TE definitely attributed to extended interval[b]	1
# of events with TE probably attributed to extended interval[c]	0
# of events with TE possibly attributed to extended interval[d]	0
# of events with TE unlikely/unrelated to extended interval[e]	1
Major bleeding events (# events)	6
# of participants with major bleeding events	6 (12)
# of events with bleeding definitely attributed to extended interval[b]	0
# of events with bleeding probably attributed to extended interval[c]	0
# of events with bleeding possibly attributed to extended interval[d]	1
# of events with bleeding unlikely/unrelated to extended interval[e]	5
Serious bleeding events (# events)	22
# of participants with serious bleeding events	16 (32)
# of events with bleeding definitely attributed to extended interval[b]	0
# of events with bleeding probably attributed to extended interval[c]	0
# of events with bleeding possibly attributed to extended interval[d]	7
# of events with bleeding unlikely/unrelated to extended interval[e]	15
Minor bleeding (# events)	33
Bleeding due to minor skin trauma[f]	17
# of serious bleeding events due to minor skin trauma	9
# of participants with any bleeding event	25 (50)

TE thromboembolism

[a]Extended interval for this analysis was defined as 7–8 weeks or 11–12 weeks between INR visits. A high or low INR did not occur more than once in a participant

[b]An event with a definite level of attribution included being on the extended interval at the time of the event or within 6 weeks of the event with an INR outside of the target range with a definite relationship to hemostasis (i.e. a high INR with a bleeding event)

[c]An event with a probable level of attribution included being on the extended interval at the time of the event or within 6 weeks of the event with an INR outside of the target range with a possible relationship to hemostasis

[d]An event with a possible level of attribution included being on the extended interval at the time of the event or within 6 weeks of the event with an INR inside or outside of the target range without a relationship to hemostasis (e.g. a low INR with a bleeding event)

[e]An event with an unlikely/unrelated level of attribution included participants not on an extended interval at the time of the event or within 6 weeks of the event

[f]Examples of minor skin trauma included lacerations, ecchymosis due to falling, bleeding gums due to brushing teeth or a chipped tooth, or bleeding after a minor procedure (e.g. wart removal, dental work, ear cleaning)

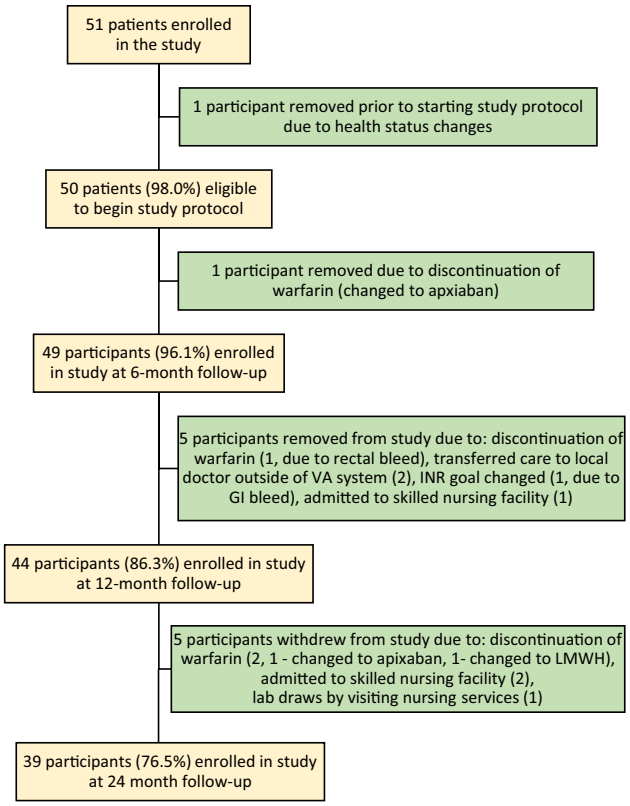


Fig. 2 Participant flow through study

participants with a warfarin dose change. There was not a statistically significant difference in number of procedures requiring warfarin interruption during the study compared to baseline (0.39 vs. 0.45, p = 0.65 at 12 months). In a post-hoc analysis comparing baseline demographics of those who were scheduled for at least 4 consecutive 12-week intervals and those who were not, statistically significant differences included past medical history of heart failure (0 vs. 10, p = 0.022), a longer duration of stable warfarin dose at baseline (109.7 vs. 84.6 weeks, p = 0.0380), and HAS-BLED (1.3 vs. 2, p = 0.0058) and Charlson Comorbidity Index (3.4 vs. 4.7, p = 0.0067) scores (Table 1).

In the primary intention-to-treat analysis for TTR, there was a 12.2% (sd. 26.4) decrease at 6 months (p = 0.12), a 7.3% (sd. 18.3) decrease at 12 months (p = 0.11), and a 4.4% (sd. 13.2) decrease at 24 months (p = 0.032) when compared to baseline (See Supplement Fig. 1; Supplement Table 1).

There were two thromboembolic events that occurred in one participant, with one event attributed to an extended INR interval. There were 28 major and serious bleeding events in 19 participants; 8 occurred while on the extended INR interval, although definite attribution to the interval could not be concluded (Table 2).

Discussion

Our study advocates the use of a detailed protocol to safely extend the INR interval and offers guidance on longer-term use of an extended INR interval to complement what previous literature has described [12, 13]. Our study found that by titrating the INR follow-up interval up to 12 weeks we could identify individuals who could not maintain an extended INR interval despite a previous history of warfarin dose stability. This titration was valued by study staff and reassured them that appropriate patients were having their INR interval extended,[16] as 28% of patients were never scheduled for a 12-week INR interval follow-up. This study had a rigorous protocol including extensive and objective inclusion and exclusion criteria and participants remained in the study despite various situations including out-of-range INRs, hospitalizations, drug–drug interactions, and bleeding.

This intervention needs to be undertaken with patients after a thorough discussion of risk and benefit. This is supported by almost one-third of participants meeting an exclusion criteria at one point during the study where it was no longer safe to extend their INR follow-up interval. While this was unexpected from our hypothesis given the prior warfarin dose stability of participants, it is consistent with prior literature that an increase in comorbidities can decrease INR stability [17, 18]. Additionally, Carris et al. found only 23% of participants able to receive 12-week INR follow-up intervals for a year [12].

Information from the extended length of this study is consistent with prior observations that past stability does not predict future stability as almost half of our study participants experienced a permanent warfarin dose change during the study [19]. Previously identified predictors of very stable INR control for patients on long-term anticoagulation with warfarin include age greater than 70 years, male gender, INR target less than 3.0, good adherence, and absence of heart failure, diabetes, gastrointestinal illnesses, or other chronic diseases [17, 18, 20, 21]. In our study, a diagnosis of heart failure was implicated with poor control on the intervention as none of the patients with this diagnosis could maintain the 12-week INR follow-up interval for 1 year. Carris et al. suggested there may be a correlation between length of time on their previous warfarin dose and the participants' likelihood of maintaining a 12-week INR follow-up interval [12]. However, in our study where participants had a longer duration of time on their stable warfarin dose and a 24-month study period, there was still difficulty in maintaining 12-week intervals, which suggests that even with long-term stability, an extended INR interval is not guaranteed to succeed.

While there was a large initial decrease in TTR, this may be an artifact unrelated to an extended INR interval.

Table 2 Demographics

	All participants (n = 50)	Participants without 4 Consecutive 12-Week Intervals (n = 35)	Participants with 4 Consecutive 12-Week Intervals (n = 15)	p value
Age	71.4 ± 7.6 Median = 69.5	72.1 ± 7.7 Median = 71	69.8 ± 7.5 Median = 68	0.3025
Distance from primary lab site, miles	17.0 ± 17.6 Range 0.3–81	17.0 ± 16.5 Range 0.3–68	17.3 ± 20.5 Range 1–81	0.9662
Indication				
Atrial fibrillation/flutter	38 (76)	29 (83)	9 (60)	0.146
$CHADS_2$ score	2.1 ± 0.9 (n = 38)	2.1 ± 0.9 (n = 29)	1.9 ± 0.8	0.4906
CHA_2DS_2-VASc score	3.2 ± 0.9 (n = 38)	3.3 ± 0.9 (n = 29)	3 ± 1	0.3675
Deep vein thrombosis	8 (16)	6 (17)	2 (13)	1.000
Hypercoagulable state	2 (4)	1 (3)	1 (7)	0.514
Mechanical heart valve	0 (0)	0 (0)	0 (0)	
Peripheral vascular disease	0 (0)	0 (0)	0 (0)	
Pulmonary embolism	6 (12)	4 (11)	2 (13)	1.000
Stroke	2 (4)	1 (3)	1 (7)	0.514
Systemic embolism	0 (0)	0 (0)	0 (0)	
Transient ischemic attack	1 (2)	0 (0)	1 (7)	0.300
Other (CAD, portal vein thrombosis)	2 (4)	1 (3)	1 (7)	0.514
Past Medical History				
Coronary artery disease	18 (36)	14 (40)	4 (27)	0.523
Congestive heart failure	10 (20)	10 (29)	0 (0)	0.022
Deep vein thrombosis	8 (16)	6 (17)	2 (13)	1.000
Diabetes mellitus	16 (32)	13 (37)	3 (20)	0.328
Hypertension	43 (86)	30 (86)	13 (87)	1.000
Major bleeding event	2 (4)	2 (6)	0 (0)	1.000
Peripheral artery disease	2 (4)	1 (3)	1 (7)	0.514
Pulmonary embolism	6 (12)	4 (11)	2 (13)	1.000
Stroke	5 (10)	3 (9)	2 (13)	0.629
Systemic embolism	1 (2)	1 (3)	0 (0)	1.000
Transient ischemic attack	1 (2)	0 (0)	1 (7)	0.300
No past medical history of significance	0 (0)	0 (0)	0 (0)	
HAS-BLED score	1.8 ± 0.9	2 ± 0.9	1.3 ± 0.7	0.0058
Charlson Comorbidity Index	4.3 ± 1.8	4.7 ± 1.7	3.4 ± 1.5	0.0067
Average weekly warfarin dose	38.5 ± 13.9 Range: 12–65 mg/week	40.4 ± 13.3 Range: 20–65 mg/week	34 ± 14.8 Range: 12–60 mg/week	0.1377
Weeks on warfarin dose	92.1 ± 68.6 Median = 67.1 Range: 28.7–340	84.6 ± 71.1 Median = 51.4 Range: 28.7–340	109.7 ± 60.8 Median = 86.1 Range: 45.1-246.1	0.0380

Given the extreme stability of study participants on their warfarin dose at baseline [12, 19], it is likely that some regression to the mean may be impacting the results of this study [22, 23]. This statistical phenomenon would predict decreased stability during the study which may negatively impact the TTR when comparing from baseline to the end of study. While this study was not powered to detect a difference in TTR, Schulman et al. also found a decrease in TTR in the 12-week follow-up group compared to control [13].

While the bleeding rates appear higher in our study than in other similar interventions,[12, 13] we do not believe it was due to the use of an extended INR interval. Possible reasons for this difference include varying definitions for major bleeding between the studies, our patients had a higher rate of dual antithrombotics with antiplatelet use, and a high number of bleeding events, both classified as minor and serious, due to minor skin trauma such as cuts and falls.

Limitations

Our study had several limitations. TTR was calculated using all laboratory data known to the study site, which may have included INRs around the time of hospitalizations and procedures. This may have decreased TTRs during the study due to factors not related to the extended INR interval intervention. Additionally, we may be missing INRs when participants were hospitalized or had a procedure at facilities other than the study site.

More importantly, this study was completed at a single center without a control arm in a Veteran population with a relatively small sample size. However, the results of this cohort have been consistent with other literature [8, 12] and could be used to power a future randomized controlled trial to validate the safety and effectiveness of an extended INR interval. A trial such as this could help to determine suitable patients for this intervention and also to determine cost effectiveness.

Conclusions

Based on 2 years of monitoring, a 12-week INR follow-up interval using a detailed protocol with titration of INR interval extension appears feasible for a subset of patients. However, risk versus benefit should be assessed with an understanding that warfarin dose and INR stability may not be maintained. At this time, patients with heart failure may not be good candidates for an extended INR follow-up interval.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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